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10/518,640	12/20/2004	Masayuki Furuya	1034232-000029	2846
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EXAMINER KRISHNAN, GANAPATHY				
ART UNIT		PAPER NUMBER		
1623				
NOTIFICATION DATE		DELIVERY MODE		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary

Application No.

10/518,640

Applicant(s)

FURUYA ET AL.

Examiner

Ganapathy Krishnan

Art Unit

1623

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 September 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 21-23 and 28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 21-23 and 28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SI/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

A Request for Continued Examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 9/11/2008 has been entered.

The Request for Continued Examination filed 9/11/2008 has been carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 2-20 and 24-27 have been cancelled
 2. Claim 1 has been amended.
 3. Remarks drawn to rejections under 35 USC 103 maintained in the previous action and a Declaration under 37 CFR 1.132 by Mr. Nagatomo.
- Claims 1, 21-23 and 28 are pending in the case.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 21-23 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toshiyuki et al (JP 62-263194, English translation; document listed in IDS of Aug. 23, 2005) in view of Yujiro et al (JP 2000-319116, English translation; listed in IDS of Aug. 23, 2005) both of record and March et al (General Organic & Biochemistry, 5th Ed., 1998, page 464).

Toshiyuki et al teach a process of making a glycoside wherein pentaacetyl glucose (a sugar molecule having an acetyl group attached to the anomeric carbon) is reacted with hydroquinone (a dihydroxy phenol) in the presence of p-toluenesulfonic acid as catalyst in xylene, to give the corresponding glycoside (page 1, see below the sub heading-Prior art; page 3, paragraphs 8-10; comparative example 2, at page 5). Even though the term hydroquinone suggests that it is a ketone, the compound exists as a tautomer between a p-diketone and p-dihydroxy benzene, which is a phenolic compound with two hydroxyl groups. It reacts with pentaacetyl glucose via the dihydroxy tautomer to give the corresponding glycoside. The

removal of acetic acid under vacuum (lower temperature) is suggested (page 3, paragraph 9).

However, Toshiyuki et al do not teach the use of Lewis acid catalyst like boron trifluoride (even though tin tetrachloride is suggested) in their process.

Yujiro et al, drawn to gallic acid derivatives, teach the preparation of a glucoside derivative via the reaction of gallic acid (trihydroxy benzoic acid) or its ester (structure (2) in claim 11) with saccharide, including pentaacetyl glucose, that is completely acetylated, in the presence of Lewis acid catalyst, one of which is boron trifluoride etherate to give the corresponding glycoside (page 3, paragraph 0011; page 4, paragraph 0018). However, Yujiro et al do not exemplify their process using xylene as the solvent.

According to March et al a carboxylic acid like propionic acid (adjacent homolog of acetic acid produced in the instant method) reacts with a phenolic hydroxyl (reaction (b) as shown in March et al) in the presence of acid catalyst to give the corresponding ester. This means that this same type of esterification can also take place in the instant method between the acetic acid generated during the reaction of the first mole of glucose pentaacetate with the gallic acid ester with the monoglycoside formed in the first step to acetylated the phenolic OH. This is a side reaction that would prevent the formation of the diglycoside. In order to avoid this side reaction and facilitate the formation of the diglycoside as in instant claim 1 the acetic acid generated has to be removed from the reaction system. This will be recognized by one of ordinary skill in the art and hence one would remove the acetic acid from the system during the process.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the process as instantly claimed and taught by the prior art for making the

glycoside as instantly claimed since the process for making such a glycoside using closely analogous starting materials, solvents and catalyst is taught in the prior art.

One of skill in the art would be motivated to use the method as instantly claimed, especially using boron trifluoride and xylene as solvent since the use of benzene as a solvent has a problem with temperature and pressure requirements for the removal of the acetic acid that is generated in the process and control of the reaction is difficult and yield is low (Toshiyuki: page 1, last paragraph though page 2, paragraph 2). Hence one of skill in the art would look for other closely related solvents and Lewis acid catalyst like boron trifluoride in order to have better control of the reaction, easy removal of acetic acid and also improve the yield. It is well within the skill of the artisan to adjust process conditions for the purpose of optimization and to use other derivatives of the phenolic compound as instantly claimed in claims 2-3, in order to extend the scope of the instant method.

Even though, Toshiyuki discloses (page 2, paragraph 3; page 5, comparative examples 2-3) that Wolf from suggests xylene as solvent the yield is about 50%, one of skill in the art would be motivated to substitute other Lewis acid catalyst like boron trifluoride as suggested by Yujiro still using xylene as solvent in order to improve the yield since xylene has been successfully used as the reaction solvent. One of skill in the art would adjust the pressure and temperature for removal of the acetic acid that is formed in the process and thereby look for improvement in the yield of the desired product, with a reasonable expectation of success.

Response to Applicants Arguments

Applicants have traversed the rejection under 35 USC 103 arguing that:

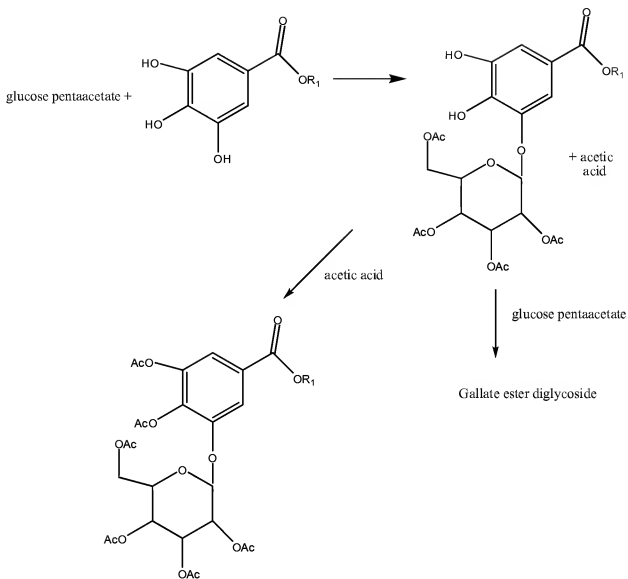
1. As shown in the Declaration of Mr. Nagatomo, Experiment 5 which corresponds to the method of Toshiyuki et al, produces high yield of a mono-glycoside compound. Experiment 4 in the said Declaration, which corresponds to the instant method produces high yields of the diglycoside compound. The difference in the results in Experiments 4 and 5 is due to reaction temperature and concentration of acetic acid in the reaction system during the reaction.

2. Experiments 2 and 3 in the Declaration, which use conditions that are outside the scope of the instant invention produce mono glycoside as the main product.

3. According to applicants they have discovered that there is an equilibrium between the gallic acid methyl ester (starting material), mono-glycoside and diglycoside based on the concentration of the byproduct and acetic acid. Surprisingly the equilibrium will be shifted to produce the diglycoside when acetic acid has been removed. Toshiyuki does not teach or suggest the temperature range as instantly claimed and discloses a method for making the monoglycoside compound and not a diglycoside.

Applicants' arguments and the Declaration of Mr. Nagatomo have been considered but they are not found to be persuasive.

The reactions taking place in the instant method is depicted below:



First of all, the product as instantly claimed is made by reacting gallic acid methyl ester with glucose pentaacetate. The first step in this reaction is the formation of the monoglycoside of gallic acid methyl ester and acetic acid (by-product). Now, in order to form the diglycoside, the monoglycoside of gallic acid methyl ester should react with a second mole of glucose pentaacetate. This second step will also generate acetic acid as a by product. Since gallic

acid methyl ester moiety in the monoglycoside product has two unreacted OH groups, these OH groups can react with the acetic acid generated to form the acylated monoglycoside (shown at the bottom left in the reaction scheme above). This would be a competing side reaction (leading to an unwanted product) in addition to the reaction of the second mole of glucosепentaacetate to form the diglycoside (desired product). The reaction of acetic acid with the OH group of the gallic acid methyl ester moiety of the monoglycoside to give the unwanted by product is an esterification reaction (reaction between acetic acid and an alcohol). This is a fundamental reaction in organic chemistry as taught by March et al above and also well known to one of ordinary skill in the art. In order to prevent this unwanted side reaction from taking place in the system the skilled artisan knows that the acetic acid that is generated in the system should be removed as and when it is formed. One of skill in the art will also recognize that the acetic acid formed can also react with the gallate ester (starting material) and prevent the formation of the monoglycoside of the gallate ester. This would be a second competing reaction, both of which will lower the yield of the desired diglycoside. The removal of acetic acid under reduced pressure is taught in the prior art of record in an analogous reaction (Toshiyuki, page 3, paragraph 9). Moreover, Toshiyuki (comparative example 1, page 4) teaches that an analogous reaction when performed at higher temperature gives low yields and also causes the browning of the product. So, one of ordinary skill in the art would want to remove the acetic acid and keep its concentration below 1.0 % or even less in order to suppress the unwanted reaction of the monoglycoside with the acetic acid since this prevents the addition of a second glucose unit to the gallic acid part to form the desired diglycoside. Based on the teaching regarding the browning of the product and also low yields obtained, one of skill in the art would want to run

the reaction at a lower temperature. Also it is well known to the skilled artisan that using reduced pressure will lower the boiling point of acetic acid and this will help remove it by distillation at a lower temperature as and when it is formed in the reaction system. The lower temperature will also avoid the browning of the product. The prior art may not have taught the temperature range as instantly claimed. It is well within the skill level of the artisan to adjust the temperature and pressure of the reaction to an optimal level such that the reaction proceeds at a reasonable rate and also the temperature at which the reaction is performed is high enough to distill the acetic acid out of the system without causing the browning of the product.

Applicants showing that Experiments 2 and 3 which use conditions outside the scope of the instant invention give the monoglycoside as the main product is also an expected result. In these two experiments the acetic acid is not removed to the extent that it would prevent the unwanted side reaction from taking place. Since it is present in the reaction system in a high enough concentration it will still react with the hydroxyl group of the gallic acid methylester monoglycoside to form the acylated derivative. Since this reaction consumes some of the gallic acid methylester monoglycoside, the amount of gallic acid methylester monoglycoside available to react with a second mole of glucose pentaacetate is reduced and hence the low yield of the diglycoside.

Therefore, applicants' assertion that they have discovered that there is an equilibrium between the gallic acid methyl ester, mono glycoside and diglycoside based on the concentration of acetic acid by-product and that the removal of acetic acid under the conditions as instantly claimed, is not an unexpected discovery. It is a well known fact based on the type of reaction taking place. This is also well known to one of ordinary skill in the art and the skilled artisan will

recognize all of this from the teaching of the prior art and his or her own general knowledge. Toshiyuki may not teach the formation of a diglycoside compound. But the skilled artisan knows that his teaching can be extended to the preparation of the diglycoside compound as instantly claimed since the chemistry is the same and requires the use of an excess of the glucose pentaacetate to react with the monoglycoside in a second step to form the desired diglycoside. There is a suggestion in the prior art that the instant method can be used to make the product of instant formula (3) with a reasonable expectation of success.

Conclusion

Claims 1, 21-23 and 28 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, Art Unit 1623

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